

A Combined Analysis of North American Case-Control Studies of Residential Radon and Lung Cancer: An Update

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Cellular mutagenesis studies, experimental research in several animal species, and epidemiological studies of underground miners have established radon as a human carcinogen (1). While results of miner studies are unambiguous in demonstrating an excess risk from radon exposure, airborne contaminants in mines, differences in breathing characteristics of miners and residents at home, and other differences in the environments of mines and homes are substantial. The miner studies provide no direct information on lung cancer risks from exposure to radon in females or children. Thus it is important to evaluate directly whether residential radon exposure is associated with lung cancer risk (2) and to confirm the extent to which exposure-related risks in mines and homes are comparable.

To date, 18 case-control studies of residential radon and lung cancer have been published, including seven studies in North America, nine in Europe, and two in China (Table 1). Studies involved from 161 to 1,449 cases, with most studies comprised of between 400 and 1,000 cases. Some of these studies reported a positive or weakly positive association between lung cancer risk and residential radon concentration, while others have reported results consistent with no association. To date, no case-control study has reported a statistically significant negative association.

In 1989, the U.S. Department of Energy (DOE) and the Commission of the European Communities (CEC) sponsored a workshop in Arlington, VA, that brought together investigators who had ongoing or planned studies of lung cancer and residential radon to establish a common working

TABLE 1
Case-Control Studies of Residential Radon and Lung Cancer

Region	No. of cases	No. of controls	Average radon concentration (Bq/m ³)	Reference
North American				
New Jersey (NJ)	480	442	29	(14)
Winnipeg (Winn)	738	738	141	(8)
Missouri-I (MO-I)	538	1,183	63	(9)
Missouri-II (MO-II)	512	553	55	(10)
Iowa (IA)	413	614	129 ^a	(11)
Connecticut (CT)	963	949	33	(13)
Utah-South Idaho (UT-ID)	511	862	57	(13)
Europe				
Sweden (Stockholm)	198	379	133	(17)
Sweden (national)	969	2,054	96	(18)
South Finland	161	328	213	(19)
Finland (national)	863	1,166	102	(20)
South West England	960	3,126	55	(21)
Italy	387	406	94 ^a	(22)
East Germany	1,053	1,667	75	(23)
West Germany	1,449	3,746	50	(24)
Sweden (non-smokers)	258	487	75	footnote 2
France	552	1,103	148	Pending
Czech Republic	206	824	519	Pending
China				
Shenyang	308	356	85 ^b	(25)
Gansu	768	1,659	223	(26)

^a Geometric mean household radon.

^b Median household radon level.

framework for the pooling of radon data (3). Investigators recognized that the excess risk due to radon would likely be small, and that because the characterization of historical exposure to radon is problematic and subject to misclassification, large sample sizes would be required to demonstrate a significant excess risk, evaluate subtle patterns of variation in radon risk, and verify extrapolations of risk from miner-based exposure-response models. In 1991 and 1995, the DOE and CEC sponsored subsequent workshops in Arlington and Baltimore to continue the process of harmonizing design protocols to facilitate the eventual pooling of data (4–6). These meetings encouraged a collaborative environment among investigators and established a common set of variables and exposure assessment procedures that provided flexibility to the collaborating investigators to tailor study design to the unique aspects of their study populations.

Officials from Health Canada hosted a subsequent planning meeting in October 1995, including the principal investigators for all completed and ongoing North American case-control studies, invited scientists with expertise in radon risk assessment, and representatives from the U.S. DOE, the CEC, and the European pooling project. The common data format was developed by the principal investigators for the North American case-control studies at the working group meetings. After a subsequent planning meeting hosted by Health Canada in June 1997, the data available from the three completed North American case-control studies were included in a pilot analysis.¹

The North American pooling project included investigators from the

six primary North American case-control studies conducted in New Jersey (7), Winnipeg (8), Missouri-I (9), Missouri-II (10), Iowa (11, 12), and Connecticut/Utah-South Idaho (13). While the Connecticut/Utah-South Idaho study was designed as a single study with common features, we included subjects for Connecticut and Utah-South Idaho separately in the pooled analysis and present the results separately, effectively leading to seven studies in North America.

A final data format for the analysis included age, year of case and control ascertainment, source of information, sex, ethnicity, home sequence identifier, radon concentration in living areas and in basements, radon estimation method, proportion of time spent in the home, smoking, family income, and education. The values of some of these variables (such as education and income) were determined at the time of enrollment of the subjects; others (such as residential radon concentration) were determined on a year-by-year basis in each of the 50 years prior to enrollment. Not all information was available for all subjects and all studies; however, this format served as the basis for merging of data and developing the analytical file that served as the basis for the combined analysis.

The North American pooling examines data on residential radon exposure and lung cancer for 4,420 cases and 5,707 controls. This extensive database permits a more detailed examination of radon and lung cancer risk and its potential modifiers than has previously been possible. The specific goals of the analysis of pooled data from studies of indoor radon and lung cancer are as follows: (1) to test the null hypothesis that residential radon does not increase risk of lung cancer; (2) if there is evidence for excess risk, to evaluate the consistency of effects among the different studies; (3) to evaluate variations in the exposure-response relationship with other lung cancer risk factors; and (4) to compare risk estimates from the pooled residential data with extrapolations from miner-based risk models, where typical exposures were higher.

Characteristics of the subjects participating in the seven North American case-control studies that form the basis for the present combined analyses are given in Table 2. In all studies, cases were ascertained

¹ V. S. Catalan, Analysis of the combined primary data from case-control studies of residential radon and lung cancer: A pilot study of three North American sites. Ph.D. Thesis, Department of Epidemiology and Biostatistics, McGill University, Montreal, 1998.

² F. Lagarde, R. Falk, K. Almren, L. Damber, F. Nyberg, H. Svensson and G. Pershagen, Glass-based exposure assessment and lung cancer risk. Doctoral dissertation, Karolinska Institutet, Stockholm, Sweden, 2001.

TABLE 2
Characteristics of North American Case-Control Studies of Residential Radon and Lung Cancer

Study	Source of subjects		Years of ascertainment	Matching	Histological diagnosis	Subject selection	
	Cases	Controls				Cases	Controls
NJ	1. Rapid reporting system with hospital pathology depts. 2. Hospital pathology records, state cancer registry, and certificate files	Controls matched for live cases and matching of controls to cases for deceased cases. 1. Live cases: driver license (<65 years); medicare files (65+) 2. Deceased cases: Death certificates	Cases: 1982–1984 Controls: 1982–1983	Respondent type (P); 1. Live (Direct): age and race (FM) 2. Deceased (Proxy); age, race, closest date of death (P)	Histological type relied on outside pathology reports.	480 Females = 48% of 994 interviewed, 37% of 1306 eligible No radon measurements were available for an additional 87 homes	442 Females = 44% of 995 interviewed, 30% of 1449 eligible
Winn	Manitoba Registry	Phone directory	Cases 1983–1990 Controls; 1983–1990	Age (P) Sex (P)	Histological confirmation relied on outside pathology reports	488 M 250 F 53% of 1400 eligible	488 M 250 F <54% of eligible
MO-I	Missouri Cancer Registry	Driver license (30–64 years) Medicare files (65–84 years)	Cases 1986–1991 Controls 1986–1991	Age (FM)	Precise histological confirmation by independent review of 76% of the cases	538 F 83% of 650 eligible completed phone questionnaire and had dosimetry from at least one home	1183 F 78% of the 1587 eligible completed phone questionnaire and had dosimetry from at least 1 home
MO-II	Missouri Cancer Registry	Driver license (30–64 years) Medicare files (65–84 years)	Cases 1993–1994 Controls 1993–1994	2-stage randomized recruitment procedure; Age, sex, smoking status (F)	Precise histological confirmation by independent review of over 80% of the cases	512 F 69% of 742 eligible cases completed questionnaires and had some dosimetry ^a	553 F 3886 initially eligible 75% of 730 targeted had both interview and some dosimetry ^a
IA	Iowa SEER Cancer Registry with 90% of subjects rapidly reported	Driver license (40–64 years) Medicare files (65–84 years)	Cases 1993–1996 Controls 1993–1996	Age (FM)	Precise histological confirmation by independent review of 96% of the cases	413 F 68% of 603 eligible completed questionnaires and had complete dosimetry	614 F 46% of 1337 eligible completed questionnaires and had complete dosimetry
CT	Cancer registries and medical record review	Random telephone screening	Cases 1989–1992 Controls 1990–1993	Randomized recruitment was used to identify cases and controls that were similar in age, sex and smoking status (FM)	Histological confirmation relied on outside pathology reports	527 M, 436, F 75% of 5,216 cases screened for eligibility 963 (79%) qualifying cases completed the study ^a	442 M, 507 F 83% of randomly selected households screened. 949% (62% of eligible controls completed the study ^a)
UT-ID	Cancer registries and medical record review	Random telephone screening	Cases 1989–1992 Controls 1989–1992	Randomized recruitment was used to identify cases and controls that were similar in age, sex and smoking status (FM)	Histological confirmation relied on outside pathology reports	319 M, 192 F 81% of 1,388 cases screened for eligibility 511 (85%) of eligible cases completed the study ^a	587 M, 275 F 94% of randomized selected households screened for eligible controls <65. 91% of HCFA sample (>65) screened 862 completed the study ^a , 85% of eligible RDD controls and 78% of eligible HCFA controls

Notes. F: Female-restricted study, M and F: Males and females included; FM: Frequency matching; P: Pairwise matching.

^a Many subjects were excluded who did not pass smoking randomization and other study criteria.

TABLE 3
Radon Dosimetry in the North American Case-Control Studies of Residential Radon and Lung Cancer

Study	Duration and method	Residence inclusion criteria	Location of dosimeter placement	Exposure time window	Exposure time window (ETW) coverage	Method of imputing missing data
NJ	1 year ATD T, some short-term charcoal canister detectors and TLDs ^a	Last NJ residence of ± 10 years during the period 10–30 years prior to diagnosis or selection.	Living area (76%); basement (5%); 4 day charcoal canister (8%) ^a	5–30 years prior to diagnosis or selection	Only 1 residence monitored first phase of study; Median ETW residence time in years: 20 years (cases) and 21 years (controls); 82% cases and 79% controls resident >15 years	Median value of controls assigned for periods not residing in index home; apartments assigned 0.4 pCi/liter
Winn	1 year ATD G	All Winnipeg residence of ± 1 year during index period	Bedroom and basement (reported separately)	5–30 and 5–15 years prior to interview	33% of eligible residences monitored; Mean years covered: 17 in 5–30 years ETW (68% of person-time); 8 in the 5–15 year ETW (80% of person-time)	Calibration to bedroom or basement monitored; if no measurement, average study value for all subjects
MO-I	1 year ATD T	All in-state index period residences	Bedroom and kitchen area	5–30 years prior to interview	Average coverage of 20 years; ETW coverage: living cases: 78.5%; deceased cases: 76%; controls: 78.8%	Stratum-specific mean (cases and controls assigned the respective group mean)
MO-II	20+ years RSM 1 year ATD	All in-state index period residences	Bedroom and kitchen (each other no differences for both method, but values by RSM significantly higher than that by ATD)	5–25 years prior to diagnosis for cases and interview for controls	Average coverage of 18.2 years in ETW; ETW coverage: 91% for cases and controls using at least one of the detectors; only 9% of pertinent years in need of imputation for missing radon values.	Annual means were used for imputation of missing values for both measure methods
IA	1 year ATD T RRD Outdoor ATD M	Current home only—limited subjects to those subjects occupying the current home for at least the past 20 years.	Each level of home, bedrooms and work areas of home including outdoor regional radon concentrations. RRD results will be available in near future.	5–19 years prior to diagnosis for cases and interview for controls	100% coverage of exposure time window. All homes were measured. Median coverage 32 years.	No missing home radon measurements period over exposure time window. No imputation.
CT	1 year ADT T	All homes occupied for at least 1 year since age 25	Bedroom, another room on lowest living area and some basements depending on occupancy. A sample of homes measured every level.	Age 25 up to 5 years prior to diagnosis	Maximum window, age 25 up to 5 years before diagnosis/interview. Analysis window, 5–25 years prior to diagnosis/interview. Average coverage for eligible homes was 57% for the maximum window and 69% for the analysis window.	The percentage time coverage for the maximum window was 69% and 79% for the analysis window. Regression trees aided in providing stratum-specific control means for imputation.

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TABLE 3
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Study	Duration and method	Residence inclusion criteria	Location of dosimeter placement	Exposure time window	Exposure time window (ETW) coverage	Method of imputing missing data
UT/S. ID	1 year ATD T	All homes occupied for at least 1 year since age 25	Bedroom, another room on lowest living area and some basements depending on occupancy. A sample of homes measured every level.	Age 25 up to 5 years prior to diagnosis	Maximum window, age 25 up to 5 years before diagnosis/interview. Analysis window, 5–25 years prior to diagnosis/interview. 62% of homes in maximum window and 78% of homes in analysis window measured.	The percent time coverage for the maximum window was 73% and 82% for the analysis window. Regression trees aided in providing stratum specific control means for imputation.

Notes. Abbreviations: ATD T: α -particle track detector manufactured and read by Terradex Corporation; ATD G: Government office responsible for dosimeter provision; ATD M: α -particle track detector manufactured and read by the Minnesota Radon Project; CONC: Only radon concentration in the one monitored home considered; CUM: Exposures were cumulated over the ETW; ETW: Exposure time window; RRD: Glass-based Retrospective Reconstruction Detector; RSM: Glass-based Retrospective Surface Monitor; TWAC: Analysis was by time weighted (by residence time) averaging of measured concentrations; IMP: Results were analyzed with imputation of missing data as described.

^a The remaining 13% of monitored homes had 2-week thermoluminescent detectors, from which regression analysis was used to estimate annual radon concentrations.

through state and provincial cancer registries and were confirmed histologically. New Jersey and Iowa identified cases through rigid reporting criteria based on hospital pathology records and death certificates as well as the state cancer registry (7, 11, 12). In the Missouri and Iowa studies, the registry-reported histological type was verified independently by microscopic examination of the tissues by experienced pathologists.

In three of the seven studies (Connecticut, Utah-South Idaho, and Winnipeg), controls were selected by random digit dialing (8, 13). Driver's license and health care financing records were used to identify controls in Iowa (11), Missouri-I (9) and Missouri-II (10), and New Jersey (14) and for those 65 and older in Utah-South Idaho. Death certificates were used as the source of controls for proxy-interviewed cases in New Jersey.

All studies matched controls to cases on the basis of age (± 5 years) and sex (Iowa, Missouri-I, and New Jersey included only females). Race was used as a matching variable in New Jersey. Smoking status was used as a matching variable in Connecticut and Utah-South Idaho (based on smoking status 10 years prior to interview) and in Missouri-II. Frequency matching or randomized recruitment was used for control selection, except in New Jersey and Winnipeg, where pair matching was used.

All of the seven North American case-control studies used α -particle track detectors as the principal method to measure the concentration of radon progeny in indoor air (Table 3). Contemporaneous measurements were necessarily made in homes that the subjects had occupied or were currently occupying and were used as an indicator of historical radon concentrations in those homes. Detectors were placed in the living area and bedroom areas of the home in which subjects were expected to spend the majority of their time. Although investigators in the Iowa study also incorporated estimates of non-residential radon exposures (including both occupational and ambient exposures) into their overall radon exposure assessment, these non-residential exposures were not included in the combined analysis to maintain comparability with the radon dosimetry in the remaining six studies. Ignoring non-residential exposures will have some impact on the estimated lung cancer risk associated with residential radon exposures, although this effect is likely to be small (15).

In most studies, an attempt was made to monitor all in-state homes occupied for a period of at least 1 year within the exposure time window of interest. In Winnipeg, radon measurements were made in all homes occupied by study subjects within the Winnipeg metropolitan area. In

New Jersey, only the last residence occupied for at least 10 years during the period 10–30 years prior to recruitment was monitored. A small number of measurements (8%) were made using charcoal canisters rather than track detectors in New Jersey. The Iowa study also measured only one home, but the participants were required to have occupied this home for at least 20 years.

Although some investigators monitored radon in homes occupied by study subjects as much as 50 years prior to recruitment (8), the combined analysis of the seven North American case-control studies of residential radon and lung cancer focuses on the exposure time window 5–30 years prior to the index date, the period identified by the National Research Council (16) as being most relevant for lung cancer risk. Restriction of radon exposure assessment to this period presumes that neither radon exposure within 5 years of lung cancer occurrence nor exposure 30 years or more prior to the index date contributes to lung cancer risk.

The final results of the combined analysis of the seven North American residential radon case-control studies are expected by the end of 2002. Additional information on residential radon lung cancer risks will be provided by an ongoing combined analysis of European case-control studies, to be followed by a planned combined analysis of both North American and European data, as well as studies from other parts of the world including China (Table 1). Subsequent reports on the European and global pooling of residential radon lung cancer studies will serve to further clarify the magnitude of the lung cancer risk associated with radon in homes.

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